of antipsychotics smaller than that which was needed in the acute episode (though they say not less than 50%). Guidelines need to be developed on when and how slowly to reduce antipsychotics, and in whom it is appropriate to eventually stop them.

In their initial trial of the prophylactic use of antipsychotics, Leff and Wing[9] reported that these were helpful to patients with a moderate, but not those with a very good, outlook. Similarly, Correll et al accept that a significant minority of people who receive the diagnosis of schizophrenia (perhaps up to 20%) will be able to come off the drugs without disadvantage, probably because they have milder illnesses.

Leff and Wing[9] also noted that those with a very poor outcome do not benefit from continued antipsychotics. The reason that such individuals are treatment resistant is because they do not synthesize excessive striatal dopamine[6]. There appear to be two types of treatment resistance[10]. First, those who have never responded to antipsychotics and whose psychosis may not involve dopamine dysregulation. Second, those who once responded to D2 blockers but have lost this ability, possibly due to the development of dopamine supersensitivity. Correll et al ignore the evidence that prolonged administration of antipsychotics to animals cause an increase in D2 receptor numbers, and that the resultant dopamine supersensitivity causes antipsychotics to lose their efficacy[2]. They do, however, cite reports that partial dopamine agonists may have less propensity to cause dopamine supersensitivity. Once again this is an issue that demands further investigation.

Finally, we psychiatrists need to reach out to our patients and to those groups critical of antipsychotic prescribing. Doctors and patients may have different priorities; patients may put more emphasis on remaining slim rather than having voices totally eradicated, or may consider it more important to be alert enough to work rather than to have conventional thoughts. In the absence of such conversations, patients may become disillusioned with psychiatry and rely on alternatives such as the Hearing Voices Network or therapies without any evidence base.

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Long-term antipsychotic treatment of schizophrenia: does it help or hurt over a 20-year period?

Correll et al[1] argue for a positive view of the risk-benefit ratio for long-term continuous antipsychotic treatment of schizophrenia. They claim that studies of long-term outcome which show negative results are not convincing because of confounding factors. Their chief argument is that in "non-randomized, uncontrolled studies... there is a high risk of confounding by indication and reverse causation, in that greater illness severity could be the cause of continued antipsychotic treatment, rather than being the effect"[1]. The other argument is that long-term continuous use of antipsychotics does not involve significant morbidity from dopamine supersensitivity psychosis. Here we provide evidence which severely questions both of these conclusions, showing that they overestimate the benefits and underestimate the risks of long-term antipsychotic treatment.

There are at least eight studies assessing whether schizophrenia patients improve when treated longer than two-three years with antipsychotic medications. These studies have been conducted by eight different investigator groups. They include those by Wunderink et al in the Netherlands[2], our own Chicago Followup Study[3], the Suffolk County study of Kotov et al[4] in the US, and the long-term data provided by the Danish OPUS trial[5], the AESOP-10 study in England[6], the Finnish Birth Cohort Study[7], the Alberta Hospital Follow-Up Study in Western Canada[8], and the international follow-up study by Harrison et al[9]. These research programs included samples studied from 7 to 20 years. Unlike short-term studies, none of them showed positive long-term results.

Correll et al quote for support a study by Ran et al[10] favoring long-term use of antipsychotics for schizophrenia in China. However, there are many weaknesses in that study. In particular, the untreated group was selected from much older unmarried chronic rural uneducated patients, while the treated group consisted of younger married educated urban patients, some of whom had received only one short period of medication over the 14 year period, rather than being continuously medicated.

As we have noted, one argument used to explain the negative results of long-term antipsychotic treatment is that the schizophrenia patients on antipsychotics for a prolonged period are more severely ill than those not on antipsychotics. However, there are no clear features on which everyone would agree distinguishing "more severely ill people with schizophrenia". Nor is it always clear what "severity" means in relation to schizophrenia. One

frequently used criterion for severity refers to more blatant psychotic illness. However, some episodes of blatant psychosis clear up quickly and thus these psychotic patients may not be more severely ill in every respect.

Another potential criterion for severity in people with schizophrenia involves those whose disorder is more likely to be sustained over a longer period of time, or who have a poorer long-term prognosis. To control for this possible confounder, we have utilized the prognostic indices outlined by Vaillant, Stephens and Zigler. These were collected in our studies at index hospitalization. Later we compared the long-term outcome of poor-prognosis schizophrenia patients medicated with antipsychotics for 15-20 years to that of poor-prognosis patients not prescribed antipsychotics for 15-20 years. We also compared a good-prognosis sample of patients prescribed antipsychotics for 15-20 years with a good-prognosis sample of patients not prescribed antipsychotics for 15-20 years. In both comparisons, those patients not on antipsychotics for 15-20 years had fewer symptoms and better outcomes after the first 2-3 years[3].

An additional limitation of Correll et al's paper is that they do not fully address the evidence on dopamine supersensitivity psychosis from animals and from humans. They limit their discussion to short-term studies of psychotic relapse and the potential loss of antipsychotic efficacy, while ignoring the serious risk for the syndrome resulting from continuous long-term antipsychotic treatment.

The clinical picture of dopamine supersensitivity psychosis is well defined and occurs with increasing frequency after two to three years of continuous antipsychotic maintenance use. Studies indicate that the syndrome manifests in 70% of patients with treatment resistant schizophrenia[11]. Other studies show that the switch to aripiprazole, mentioned by the authors, may actually unmask and intensify psychotic symptoms previously suppressed by stronger D2 antagonists[12]. While long-term continuous use of antipsychotics may induce the syndrome, these medications also block psychotic symptoms, which therefore remain largely unrecognized until the "breakthrough" of more severe symptoms occurs and leads to treatment resistance.

While several research groups have described dopamine supersensitivity psychosis as a serious risk of long-term continuous use of antipsychotics, there has been a systematic failure to incorporate this finding into the risk-benefit ratio for continuous use of antipsychotics. The same applies to the possible negative impact of long-term antipsychotic treatment on work functioning[3]: the block of dopamine receptors may indeed reduce drive and motivation.

Unfortunately, views about the long-term efficacy of antipsychotics are often based on the results from short-term (0-2 years) evaluations. As we have highlighted, there are at least eight major studies which fail to find better outcomes for schizophrenia patients treated on a long-term basis with antipsychotics. These negative results from multiple large well-documented long-term studies are a clear warning sign.

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Disease modifying effects of antipsychotic drugs in schizophrenia: a clinical and neurobiological perspective

Only in psychiatry would the benefits of one of the great pharmacological breakthroughs in the history of medicine be questioned over a half century after its introduction to clinical practice. When H. Laborit, a French Naval Surgeon stationed in Tunisia, serendipitously realized that chlorpromazine, a compound synthesized by the chemist P. Charpentier, could be used for the treatment of schizophrenia, and brought it to the attention of J. Delay and P. Deniker, psychiatrists at St. Anne's Hospital, a chain of events ensued that changed the course of psychiatry and ushered in the age of psychopharmacology[1]. The advent of this antipsychotic prototype was of comparable significance to other therapeutic milestones like the discovery of insulin, antibiotics and L-dopa.

In the ensuing years, numerous studies by eminent researchers in many countries documented the therapeutic efficacy of chlorpromazine, and the other antipsychotics that followed, in relieving the acute psychotic symptoms of schizophrenia and preventing their recurrence[2]. And while neurological side effects were prevalent, and in many cases problematic, in most instances they could be managed with dose adjustment or adjunctive medications. Second generation ("atypical") medications in turn provided comparable or (in clozapine's case) superior efficacy, and fewer neurological but more metabolic side effects. However, in both cases, the therapeutic benefits of antipsychotics, when used properly, more than offset their side effects[3].